

REMARKS

I. Status Summary

Claims 5-7, 9-12, 14-16, 26-28, 42, and 47 are pending in the subject application and have been examined by the U.S. Patent and Trademark Office (hereinafter "the Patent Office").

Claims 12 and 15 have been objected to as being dependent on a rejected base claim.

Claims 5-7, 9-11, 14, 16, 26-28, 42, and 47 have been rejected under the written description and enablement provisions of 35 U.S.C. § 112, first paragraph.

Claims 12 and 15 have been canceled without prejudice.

Claims 42 and 47 have been amended. Support for the amendments to claims 42 and 47 can be found throughout the specification as filed, including particularly at page 17 (mutagenesis of the N-terminal domain of gamma-II-crystalline, particularly, amino acids Lys 2, Thr 4, Tyr 6, Cys 15, Glu 17, Ser 19, Arg 36 and Asp 38 not including the initiator methionine, each of which is in the N-terminal beta-sheet); page 2 ("regions and amino acids in the beta-sheet of the starting proteins, which are exposed on the surface and thus accessible to the solvent or possible binding partners, are selected" for mutagenesis); and at page 17 (description of ***Preparation of a DNA pool of mutated gamma-II-crystalline genes*** and ***Oligoassembling*** relates to making random amino acid substitutions at particular amino acid positions). Thus, no new matter has been added by the amendments to the claims.

New claims 48-57 have been added. New claims 48 and 49 correspond to objected to claims 12 and 15 rewritten in independent form. Accordingly, support for the new claims can be found in pending claims 12 and 15. Support for new claims 50-57 can be found throughout the specification as filed, including in the claims as originally filed. Additional support can be found on page 17 (eight particular amino acids that can be mutagenized in bovine gamma-II-crystallin, each of which is located with three beta-strands of the N-terminal beta-sheet of bovine gamma-II-crystallin), in the section entitled "***Oligoassembling***" beginning on page 17, and in the section entitled "***Preparation of phagemid pGCKT 8-3***" beginning on page 19, each of which

describes the preparation of libraries of mutagenized gamma-crystallins. Thus, no new matter has been added by the inclusion of the new claims.

Reconsideration of the subject U.S. patent application based on the amendments and remarks presented herein in view of the Request for Continued Examination (RCE) submitted herewith is respectfully requested.

II. Response to the Written Description Rejection

Claims 5-7, 9-11, 14, 16, 26-28, 42, and 47 have been rejected under 35 U.S.C. 112, first paragraph, upon the contention that they contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. According to the Patent Office, the claims encompasses any gamma-crystallin polypeptide mutagenized at two, or three or four of beta strands of at least one beta sheet such that the mutant possesses a new binding activity which did not exist in the parent protein. The Patent Office further asserts that the claimed genus of mutant proteins is represented by two mutants of gamma-II-crystalline of SEQ ID No. 22 having the same seven residue-mutation of residues K3, T5, Y7, C16, E18, S20, D39 into R3, K5, K7, Y16, S18, N20, L39, which involves mutations in the first three beta strands of the first (from N-terminal end) beta sheet of gamma-crystallin. This species is asserted to be the only mutation that results in acquiring "a new binding activity", which the Patent Office asserts is not sufficiently representative of the genus of any mutants of proteins encompassed by the claims.

After careful consideration of the rejection and the Patent Office's bases therefor, applicants respectfully traverse the rejection and submit the following remarks.

Initially, applicants respectfully submit that the claims have been amended to recite *inter alia* mutagenized gamma-crystallin polypeptides wherein the amino acids that are mutagenized are present on a surface of said gamma-crystallin polypeptide and are thus accessible to a solvent or a binding partner. Support for the amendment can be found in the specification as filed on page 2 ("regions and amino acids in the beta-sheet of the starting proteins, which are exposed on the surface and thus accessible to

the solvent or possible binding partners, are selected" for mutagenesis). Thus, no new matter has been added by the amendments to claims 42 and 47.

Applicants respectfully submit that the particular amino acids that are available in gamma-crystallins for mutagenesis that satisfy this criterion are few in number. In particular, applicants respectfully submit that the crystal structure of gamma-crystallin has been solved and is publicly available, and as such one of ordinary skill in the art would understand which amino acids would thus be available for mutagenesis.

Furthermore, applicants respectfully submit that given the high degree of amino acid sequence and particularly three-dimensional structure conservation among the gamma-crystallins, applicants respectfully submit that the disclosure in the instant specification of, for example, amino acids Lys 3, Thr 5, Tyr 7, Cys 16, Glu 18, Ser 20, Arg 37, and Asp 39 of bovine gamma-II-crystallin would inform one of ordinary skill in the art as to what similarly situated amino acids would be appropriate for mutagenesis in the presently disclosed subject matter.

Accordingly, claims 5-7, 9-11, 14, 16, 26-28, 42, and 47 are believed to be in compliance with the written description requirement of 35 U.S.C. §112, first paragraph. Claims 12 and 15 have been canceled, and thus the instant rejection is believed to be moot as to these claims. As such, allowance of claims 5-7, 9-11, 14, 16, 26-28, 42, and 47 is respectfully and earnestly solicited.

III. Response to the Enablement Rejection

Claims 5-7, 9-11, 14, 16, 26-28, 42, and 47 have been rejected under 35 U.S.C. 112, first paragraph, upon the contention that while the specification enables the mutants of bovine gamma-crystallin of SEQ ID NO. 22 obtained by mutations at positions identified in claim 12, it does not reasonably provide enablement for mutants of crystallins other than bovine γ -crystallin, and also does not enable other proteins with mutations at beta sheet structure as claimed.

After careful consideration of the rejection and the Patent Office's bases therefor, applicants respectfully traverse the rejection and submit the following remarks.

In support of the instant rejection, the Patent Office asserts that applicants' contention that "the specification provides substantial guidance as to the locations of

mutations” on page 9 “does not address gamma-crystallin and addresses any protein with beta-strand structures” (see Non-Final Official Action at page 6). Applicants respectfully submit that this contention, even if true, does not support the instant rejection as gamma-crystallins are proteins with beta-strand structures.

Irrespective of the above, applicants respectfully submit that the specification as filed includes specific recitations of amino acids that can be mutagenized to arrive at the instantly claimed subject matter. Examples of these amino acids are given on page 17. Additionally, and as set forth hereinabove, the three-dimensional structures of several representative gamma crystallins have been solved and are publicly available. Therefore, applicants respectfully submit that the specification as filed does indeed teach exemplary amino acids that can be mutagenized in bovine gamma-II-crystallin, and further suggests to one of ordinary skill in the art that amino acids in corresponding positions of other vertebrate gamma-crystallins would also be appropriate for mutagenesis. As such, applicants respectfully submit that one of ordinary skill in the art would further understand which amino acids are appropriate for mutagenesis based on this disclosure.

Next, applicants respectfully traverse the Patent Office’s assertion that a “surface of the protein” would not be understood by one of ordinary skill in the art. Particularly, applicants respectfully submit that contrary to the Patent Office’s assertion, the specification as filed does indeed disclose exemplary residues that are on a surface of bovine gamma-II-crystallin. These residues are disclosed *inter alia* on page 17 in the section entitled “***Selection of a suitable region for mutagenesis in gamma-crystalline***”, which discloses:

Based on the X-ray structure of gamma-II-crystalline (Wistow et al., 1983), the N-terminal domain of gamma-II-crystalline (Acc. M16894) was selected for mutagenesis. Eight amino acids in all, which form a continuous surface segment, were identified there. The selected amino acids are part of a beta-sheet and should not contribute substantially to preserving the structure. They are amino acid positions which are accessible to the solvent and thus also to possible binding partners. The eight amino acids Lys 2, Thr 4, Tyr 6, Cys 15, Glu 17, Ser 19, Arg 36 and Asp 38 comprise an area of approx. 6.1% of the total surface area of the protein.

Specification at page 17 (emphases added; note that the numbering relates to amino acids in the polypeptide minus the initiator methionine).

The Patent Office's assertion that there is no definition of "a surface" is also traversed, as the specification states on page 2 that "[b]ased on the crystal structure, regions and amino acids in the beta-sheet of the starting proteins, which are exposed on the surface and thus accessible to the solvent or possible binding partners, are selected". Therefore, applicants respectfully submit that one of ordinary skill in the art would understand that amino acids that are "exposed on the surface" are those that are "accessible to the solvent or possible binding partners", and that these amino acids can be determined by three dimensional modeling and crystal structure determination.

Therefore, since the Patent Office has conceded on page 6 of the Non-Final Official Action that "for random mutagenesis, one would not need to know which amino acids need to be changed", the Patent Office's assertion that "in the absence of guidance for which parts of the 'template molecule' are to be changed" has been mooted by the amendments to the claims and by the identification of additional support as set forth herein.

And finally, applicants respectfully submit that the specification as filed must also be considered from the perspective and with the knowledge of one of ordinary skill in the art. Applicants respectfully submit that the specification as filed teaches amino acids that are appropriate for mutagenesis in a member of a highly conserved family of proteins. This information informs one of ordinary skill in the art as to which corresponding amino acids in other gamma-crystallins would also be appropriate for mutagenesis. Given that the specification as filed includes sufficient direction to allow one of ordinary skill in the art to select which amino acids to mutagenized, that the techniques that would be required to produce such mutations are all well known to one of ordinary skill in the art, and further that techniques that would allow one of ordinary skill in the art to test various candidate mutagenized gamma-crystallins for binding to different binding partners of interest are also known to one of ordinary skill in the art, applicants respectfully submit that the Patent Office has not presented a *prima facie* of lack of enablement of claims 5-7, 9-11, 14, 16, 26-28, 42, and 47.

Summarily, applicants respectfully submit that the subject U.S. patent application provides adequate guidance and instruction such that one having ordinary skill in the art can make and use the presently disclosed subject matter as claimed in pending claims 5-7, 9-11, 14, 16, 26-28, 42, and 47. Indeed, applicants respectfully note that 35 U.S.C. §112, first paragraph, requires no more than a disclosure sufficient to enable one skilled in the art to carry out the invention commensurate in the scope of the claims, and this requirement has been met.

Accordingly, claims 7, 9, 11, 14, 16, 26-28, 42, and 47 are believed to be in compliance with the enablement requirement of 35 U.S.C. §112, first paragraph. As a result, allowance of claims 7, 9, 11, 14, 16, 26-28, 42, and 47 is respectfully and earnestly solicited.

IV. Discussion of the New Claims

New claims 48-57 have been added. New claims 48 and 49 correspond to objected to claims 12 and 15 rewritten in independent form. Accordingly, support for the new claims can be found in pending claims 12 and 15. Support for new claims 50-53 can be found throughout the specification as filed, including in the claims as originally filed. Additional support can be found on page 17 (eight particular amino acids that can be mutagenized in bovine gamma-II-crystallin, each of which is located with three beta-strands of the N-terminal beta-sheet of bovine gamma-II-crystallin), in the section entitled "***Oligoassembling***" beginning on page 17, and in the section entitled "***Preparation of phagemid pGCKT 8-3***" beginning on page 19, each of which describes the preparation of libraries of mutagenized gamma-crystallins. Thus, no new matter has been added by the inclusion of the new claims.

Applicants respectfully submit that the remarks presented hereinabove with respect to the rejections as applied to the currently pending claims are equally applicable to the new claims.

Furthermore, with respect to claims 54-57, applicants respectfully submit that these claims recite mutagenized gamma-crystallins that include substitutions in amino acids that are present on a surface of the N-terminal beta-sheet of the gamma-crystallin polypeptide. This region corresponds to the beta-sheet in which the eight specific

amino acids of bovine gamma-II-crystallin that were modified as disclosed on pages 17 *et seq.* of the instant specification are present.

As a result, applicants respectfully submit that new claims 48-57 are also in condition for allowance, and respectfully solicit a Notice of Allowance to that effect.

CONCLUSIONS

In light of the above amendments and remarks, it is respectfully submitted that claims 5-7, 9-11, 14, 16, 26-28, 42, and 47-57 of the present U.S. patent application are now in proper condition for allowance, and an early notice to such effect is earnestly solicited.

If any small matter should remain outstanding after the Patent Examiner has had an opportunity to review the above Remarks, the Patent Examiner is respectfully requested to telephone the undersigned patent attorney in order to resolve these matters.

DEPOSIT ACCOUNT

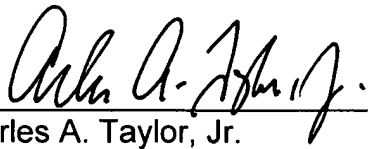
The Commissioner is hereby authorized to charge any underpayment and/or credit any overpayment of fees associated with the filing of this correspondence to Deposit Account No. 50-0426.

Respectfully submitted,

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Date: April 16, 2008

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